**APPLICANT'S REMARKS**

1. Status of the Claims

Claims 1–18 are pending.

2. Withdrawn Rejections

The Applicant gratefully acknowledges that the Examiner has withdrawn the previous rejections of:

- claims 1–4, 8, 9, and 11–17 under 35 U.S.C. 103(a) as being unpatentable over MITTENDORF in view of SZABO.
- claims 1–9 and 11–18 under 35 U.S.C. 103(a) as being unpatentable over MITTENDORF in view of SZABO and NAKAZI; and
- claims 1–4 and 8–17 under 35 U.S.C. 103(a) as being unpatentable over MITTENDORF in view of SZABO and YAMADA.

In each instance, the Examiner recognizes that SZABO does not provide sufficient motivation to combine the compound of formula (I), as provided in MITTENDORF, with cyclodextrin (CD).

3. The New Rejections

The Examiner now puts forward the same rejections of the claims based on MITTENDORF and SZABO, but with the addition of two new references, LIU and LOFFTSON. Specifically, the Examiner rejects:

- claims 1–4, 8, 9, and 11–17 under 35 U.S.C. 103(a) as being unpatentable over MITTENDORF in view of SZABO, LIU, and LOFTSSON;
- claims 1–9 and 11–18 under 35 U.S.C. 103(a) as being unpatentable over MITTENDORF in view of SZABO, LIU, LOFTSSON and NAKAZI; and
- Claims 1–4 and 8–17 under 35 U.S.C. 103(a) as being unpatentable over MITTENDORF in view of SZABO, LIU, LOFTSSON, and YAMADA.

4. The Assertion of *Prima Facie* Obviousness

The Examiner concludes that the presently claimed invention would have been obvious for one skilled in the art because (1) MITTENDORF teaches the compound of formula (I) and "suggests" the compound is water insoluble, (2) LIU and LOFTSSON teach the known technique of using CD to improve solubility of water-insoluble compounds, and (3) SZABO teaches the use of CD to improve the solubility of other compounds that have the same method of action as the compound of formula (I).

According to the Examiner, LIU discloses that the formation of CD complexes has a strong dependence on the size of the compound, so there is "some degree of predictability such that one of ordinary skill in the art would have a reasonable expectation of success in combining the prior art."

Therefore, the Applicant understands the Examiner to be arguing that one skilled in the art would reasonably predict the compound of formula (I) would complex with CD based

on the compounds of SZABO because the compound of formula (I) is "size equivalent" to the compounds of SZABO.

5. Applicant Requests Reconsideration and Withdrawn of the New Rejections

For reasons discussed in detail below, the Applicant respectfully submits that the claims of this Application are not obvious based on the cited combination of references. In particular, the Applicant respectfully submits that the cited combination of references does not provide sufficient guidance for one skilled in the art to have had a reasonable expectation of successfully combining the compound of formula (I) and cyclodextrin.

6. The Legal Test for Obviousness

The Supreme Court recently addressed the issue of obviousness in KSR International Co. v. Teleflex Inc., 127 S. Ct. 1727 (2007). The Court stated that the Graham v. John Deere Co. of Kansas City, 383 U.S. 1 (1966), factors still control an obviousness inquiry. Those factors are: 1) "the scope and content of the prior art"; 2) the "differences between the prior art and the claims"; 3) "the level of ordinary skill in the pertinent art"; and 4) objective evidence of nonobviousness. KSR, 127 S. Ct. at 1734 (quoting Graham, 383 U.S. at 17-18). KSR affirmed that §103 does not bar patentability if the improvement is "more than the predictable use of prior art elements according to their established functions."

At least some degree of predictability is required to support a *prima facie* finding of obviousness. Evidence showing there was no reasonable expectation of success may

support a conclusion of non-obviousness. The Federal Circuit for *In re* O'Farrell (853 F.2d 894, 903 (Fed. Cir. 1988)) observed that an obviousness finding was appropriate where the prior art "contained detailed enabling methodology for practicing the claimed invention, a suggestion to modify the prior art to practice the claimed invention, and evidence suggesting that it would be successful."

7. LIU and LOFTSSON Do Not Provide Reasonable Predictability

The Examiner is asserting that, because the compounds of SZABO complex with CD, and because the compounds of SZABO are of equivalent size to the compound of formula (I), and because size offers "some degree of predictability", that one skilled in the art would reasonably expect the compound of formula (I) to complex successfully with cyclodextrin (CD).

Since the Examiner acknowledges that MITTENDORF and SZABO do not make obvious the presently claimed combination–support for the Examiner's new rejections must come from LIU and LOFTSSON.

Therefore, although Applicant's Remarks are directed against the combination of references (not the references individually), nonetheless, Applicant's Remarks are primarily concerned with LIU and LOFTSSON because the Examiner's new rejections are fundamentally based on these references.

The Examiner asserts that LIU teaches that complexation of CD with a given compound "largely depends on the complexed compound's size compatibility with the dimensions of the CD cavities" (emphasis by the Examiner). The Examiner further states that LIU teaches "it is routine optimization of [the] concentration of CD to form CD:guest complexes."

The Applicant respectfully submits that the Examiner is reading LIU narrowly on the factor of "size compatibility" and not considering the extensive teaching in LIU of other factors.

The Examiner refers approving to LIU, page 115, "especially" paragraph 1, and page 116, paragraphs 2 and 4. On page 115, in paragraph 1, LIU indeed states:

> Whether or not a compound can form inclusion complexes with CDs largely depends on the compound's size compatibility with the dimensions of the CD cavities.

LIU also states:

- The stability of a complex also depends, however, on other properties of the guest molecule, such as its polarity; (page 115, paragraph 1)
- Geometry, however, certainly is not the sole factor determining the stability of a complex. (page 115, paragraph 4); and
- Certain chemical groups and substituents may greatly affect complex formation (page 115, paragraph 5).

In addition, The Examiner asserts that LOFTSSON teaches "it is routine in the art to optimize the concentration of cyclodextrin, teaching examples of 1.5, 10, 15 and 50 %w/v."

The Applicant respectfully submits that, when read in its totality, LOFTSSON supports the conclusion that CD-complexation is unpredictable.

LOFTSSON states "[t]here is no simple construct to describe the driving force for complexation." (page 1020, column 1, paragraph 1) and "prediction of compound solubilization by cyclodextrins continues to be highly empirical…" (page 1020, column 2, paragraph 2). At best, LOFTSSON provides "several general statements" (*id.*) about the solubilizing effects of cyclodextrins.

Thus, far from a "detailed enabling methodology," LIU and LOFTSSON provide an equivocal overview of CD complexing—introducing the relevant parameters, but not providing sufficient guidance on how one skilled in the art can actually predict when a given compound will, in fact, complex with CD. In other words, when read in their totality, LIU and LOFTSSON do not enable one skilled in the art to reasonably predict that a given compound will complex with CD. The skilled artisan can guess—but wishful thinking is not *prima facie* obviousness.

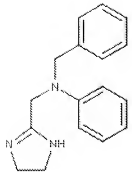
Again, the Applicant respectfully submits that CD complexing is unpredictable. Applicants base this conclusion directly on the combination of cited references, including LIU and LOFTSSON. An unpredictable technique—even a common one—cannot *per se* provide a reasonable expectation of success.

8. The Fact That the Compounds of SZABO Are "Size Compatible" With Cyclodextrin Does Not Establish That the Compound of Formula (I) Is Also "Size Compatible"

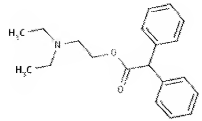
Even if the full disclosure of LIU and LOFTSSON could be ignored and "size compatibility" be used as the sole factor, there is still no reason to conclude that the compound of formula (I) is "size compatible" with CD.

Critically, neither LIU nor LOFTSSON provide any guidance for determining when two compounds are of equivalent "size compatibility" or "molecular dimension." Is "size compatibility" and/or "molecular dimension" based on 2-D conformation, 3-D conformation, molecular weight, or some other parameter? How close is close enough?

For example, LIU teaches that these compounds "should exhibit similar affinities of β-CD if only molecular dimension is considered."



Antazoline



adiphenine

"However, β-CD binds anatazoline nearly twice as strongly as it does adiphenine." (page 115, paragraph 5) No explanation is offered by LIU.

The Examiner, nonetheless, argues that the compound of formula (I) is of equivalent "size compatibility" to the compounds of SZABO. The Examiner does not provide any support for his argument—besides that fact that all three compounds have the same method of action. Yet, method of action is not relevant to size.

On the contrary, there are numerous reasons one could conclude that the compound of formula (I) is not of equivalent "size compatibility" to the compounds of SZABO, such as, for example, their differing molecular weights, chemical formulas, and functional groups.

9. Conclusion

For at least the foregoing reasons, the Applicant respectfully requests that the §103(a) rejection of the claims of this Application be reconsidered and withdrawn.

The Applicant respectfully requests favorable consideration of the foregoing Remarks and the issuance of a Notice of Allowance for this Application.

Respectfully submitted,

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